CHLOROMA AND ITS RELATION TO LEUKÆMIA.

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> " La publication des faits rares et curieux est toujours chose utile, ne fût-ce que pour indiquer aux médecines une nouvelle cause d'erreur, un nouvel écueil sur lequel leur experience peut faire naufrage. Néanmoins, tant qu'ils sont isolés, les faits de ce genre ne peuvent être considérés que comme des pierres d'attente, et ils réacquièrent de véritable importance que lorsqu'en les rapprochant de faits analogues ou identiques existant déja dans la science, ou peut les faire servir soit à constituer une espèce morbide nouvelle, soit à circonscrire, à délimiter une forme particulière de maladie offrant dans son aspect ou dans sa marche quelque chose de special."—Aran.

Some time ago I had a patient in what seemed to be the last stage of leukæmia. After death the new growths, which differed in their localization from those usually found in leukæmia, had a color so distinctly green, as distinguished from the greenish tint often seen in leukæmia, that the question arose in my mind whether the cases of "chloroma" previously reported were not leukæmic.

Not knowing that the question had already been raised, I hoped at the best to find in the original descriptions of the cases something bearing out my idea. Soon after beginning researches in the literature I discovered that my idea was not new, but had been expressed by Von Recklinghausen.[1] But, on continuing the search, I found the question by no means settled, and, as the subject has an interest far beyond the peculiar color or the rarity of chloroma, I give the results not only of the study of my own case, but also those of an exhaustive examination of the literature.

My patient was a lad (L. C.) fifteen years and nine months old. His family history, as far back as the grandparents, was without bearing on the case. He had whooping cough at three years, mumps at eleven, measles at thirteen. He never had malaria nor lived in a malarial locality. With the exceptions named, was perfectly well up to the time the present illness began. He went to school until December, 1891, when he was allowed to stay away on account of pains in his eyes while studying. At that time there was nothing abnormal in the appearance of the eyes. About the same time, before Christmas of 1891, the mother noticed that the boy, who had before a good color, was very pale. He was given quinine, presumably as a tonic. Soon after, marked shortness of breath began, with palpitation of the heart on exertion. Even before the end of the year dyspnœa was so marked that the boy "got out of breath after walking to the barn, a distance of 'about a block;' and going back, up a slight ascent, he had to stop at a stile to get his breath." At that time,

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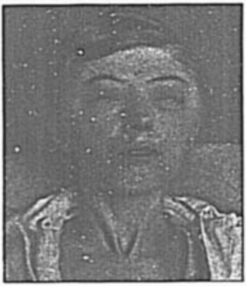
[1] Ziegler, in his Lehrbuch, 5. Aufl. i. p. 237, says: "Von Recklinghausen (Tagebl. d. Naturforscherver. in Strassburg, 1885) zählt das Chlorom in die Gruppe der hyperplastischen Lymphome (Leukämie, Pseudoleukämie, multiple Myelome) von der sie eine Spielart darstellen."

i.e., before Christmas, the mother thinks, the boy was as pale as on admission. The dyspnœa continued and became so severe that, two weeks before admission, the patient was given a bedroom on the ground floor, as he could not go up stairs without great discomfort. He never had nose-bleed before this disease came on, but since then has had three attacks, two of them quite severe, so that "he got quite faint." About the end of the year the eyes became prominent. About six weeks before admission swellings appeared in both temporal regions. These were ascribed to injuries, though there was no history of such. For some time the heart's action had been accelerated, and a month before admission exophthalmic goitre was diagnosed. For two weeks before admission the boy had been deaf, and for ten days dizzy.

Status, on admission, March 16, 1892: Undeveloped boy of slight frame; poorly nourished muscles; moderate panniculus. Skin very pale; waxy; no cyanosis; slight œdema on temples, none on the extremities; a few ecchymoses on thighs, legs, and prepuce, from one to five millimetres in diameter. Infantile sexual organs; no pubic hair. Expression anxious; scleræ bluish, visible mucous membranes very pale. On the teeth, small brownish patches and traces of fresh blood. Small ecchymoses on hard palate and velum; gums very pale, not swollen. Pinching the skin causes bluish-red discoloration, becoming dark yellow by next day. The eyes are prominent; the lids cannot be entirely closed. Above the bulbs one can feel hard masses through the upper lids. These extend from the inner to the outer canthus, are from one-fourth to one-half inch wide, project slightly in advance of the superciliary ridge, with which they form sharp angles. They are immovable, closely fitting the bulbs below, and above giving the impression of growing out from the orbital connective tissue rather than the orbital bones. They have smooth surfaces; the lids over them are dark, freely movable. The eyes project about one-quarter inch beyond the superciliary-malar line. Left pupil smaller than right; reflexes normal on both sides. Ophthalmoscopic examination (Dr. Carrow) shows hemorrhages in both retinæ—small, very numerous, accompanying the vessels; also white patches.



There are symmetrical swellings in both temporal regions, occupying all the space beneath the temporal fascia, and probably half an inch thick at the thickest part, tapering off to the edges. Owing to œdema in the skin over these swellings it is difficult to examine them. They are smooth and feel as hard as bone. There are no other tumors on the head. The thyroid gland is slightly enlarged. (This must have been of recent occurrence, as the mother had not noticed it, though told to expect it.) There is a fine but distinct thrill, and a systolic murmur over the gland.

Thorax small, but symmetrical. Percussion: right, normal; left, dulness below sixth rib in axillary line, filling Traube's space, and continuous with splenic dulness. Area does not change according to position. Absent vocal fremitus and breath-sounds over it. Respiration 26, costo-abdominal.

Apex-beat in normal position; heart dulness not enlarged; sounds faint but clear; radial pulse 126, small and soft, but regular.

Liver dulness area not enlarged, palpation normal.

Spleen can be felt three fingers' breadth below ribs, moderately hard, not painful.

Percussion over sternum causes pain.

Examination of abdomen negative. For some time there has been nausea, at times vomiting, and a very capricious appetite. The boy has taken little food during the last few weeks.

Urine 1000 c.c.; sp. gr. 1017; acid; yellow. Copious sediment of urates and phosphates, with cylindroids and small hyaline casts. No albumin or sugar. Urea 1.7 per cent.

Blood. Fresh drop shows enormous increase of colorless corpuscles, apparently as numerous as red. Red somewhat diminished, but not otherwise altered. Thoma-Zeiss shows 3,150,000 red and 743,500 white corpuscles to the cubic millimetre; Fleischl, 60 per cent. Dried and stained with eosin and methylene blue, the blood shows great increase of lymphocytes, a few large mononuclear cells with faintly staining nuclei; relatively diminished polynuclear cells, no eosinophile cells; no myelocytes; a few normoblasts.[1]

Three days after admission I made the patient the subject of a clinical lecture in the University Hospital. The diagnosis was leukæmia, based not only on the blood-finding, but also on the history and the other symptoms, viz., pallor, dyspnœa, hemorrhage, rapid heart, gastric disturbance, and eye (retinal) changes. I called attention to the fact that the enlargement of the spleen was hardly sufficient to explain the high degree of leukæmia, and as there was no enlargement of lymph glands I assumed the bone-marrow was extensively diseased. At the same time I pointed out that the blood examination, as far as it had gone, did not confirm this. The pain over the sternum I was not inclined to use as a diagnostic sign of lesion of the bone-marrow. An acute leucocytosis as the result of sarcoma I rejected on account of the long duration of symptoms of blood disease.[2]

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[1] Having no preparations ready for the Ehrlich stains we had to forego their use at the time.

[2] My first diagnosis of the case, before taking the history or examining the blood, was sarcoma of orbit (Tenon's capsule) with metastatic growths in the temporal region.

Exophthalmic goitre as a diagnosis fell to the ground as the examination proceeded. The exophthalmus, the goitre, and the heart symptoms were all explicable on other grounds; there was no tremor, no discoloration nor vasomotor change in the skin, no Graefe's nor Stellwag's symptom.

The boy's condition became rapidly worse. The temperature rose to 102° F., pulse between 120 and 180. A trace of albumin appeared in the urine. The goitre and the œdema over temporals subsided, and on the sixth day after admission the patient died. He was able to take only the smallest quantity of food (milk and lime-water, a little rare beef) during the time he was in the hospital. He had a craving for beef.

An autopsy was obtained with great difficulty, and was not complete. For it, and for valuable assistance at it as well as for the photograph from which the illustration is taken, I am indebted to my friend and colleague, Dr. W. J. Herdman. The autopsy notes (condensed) are as follows:

Section—post-mortem. Cadaver of undeveloped and emaciated boy. Marked rigor mortis; very faint discoloration on back. Skin pale, eyelids dark; on thighs and skin of penis small ecchymoses. Moderate panniculus. The periosteum of sternum is thickened and of a pale-greenish color. Omentum well preserved. Mesenteric glands slightly larger and pinker than normal. Slight excess of fluid in peritoneal cavity. Thymus weighs ten grammes, larger part 4 x 5 cm. just above arch of aorta, continuous with a narrow process extending to the cricoid cartilage. Lower part appears normal, not degenerated; upper part is homogeneous and contains a small green tumor. Thyroid not enlarged.

Lungs collapsed; heart in normal position. Left pleura contains 800 c.c. of bloody fluid. Pericardium contains normal amount of fluid; its walls thickened, especially on the left side; of pinkish color, and showing numerous subserous hemorrhages. Heart weighs eight ounces. Over left auricle numerous pale green nodules from one to five millimetres in diameter. Both ventricles contain large, firm, greenish-yellow clots, which are continuous with similar ones in the auricles and pulmonary vessels. Numerous sub-endocardial ecchymoses in both ventricles, especially left. Left lung crepitant over anterior part of upper lobe only; the rest is tough and leathery. Over the posterior part of the lower lobe there is a deposit of greenish material under the pleura and stripping off with it from one to three millimetres thick. Right lung slightly adherent behind, crepitant all over; slight hypostatic congestion in lower lobe posteriorly. The pleura has a deposit of greenish-yellow material in it similar to that in left side.

Spleen slightly enlarged; weighs 150 grammes; capsule wrinkled, of a pale pink color, with greenish shimmer. Cut surface granular, very anæmic, Malpighian bodies indistinct; larger vessels have greenish walls. A small accessory spleen has the same characteristics.

Kidneys, small (4 and 4½ ounces), smooth, very pale; section anæmic, glistening, structure not plain; cortex rather wide; in the boundary zone are numerous small greenish bodies with indistinct outlines. In the pelves small greenish-yellow bodies similar to those on the heart.

Supra-renal bodies appear normal.

Pancreas looks normal, but contains near the tail a pale-greenish body the size of a small pea.

Stomach. Mucous membrane shows thickly-set ecchymoses, especially in lesser curvature, from the size of a pin-hole to that of a pin-head; scattered over the mucous membrane are small pale greenish-yellow prominences.

The solitary glands in upper part of ileum slightly enlarged, two Peyer's patches about three feet above valve show shaven-beard appearance. Mucous membrane of colon grayish, the solitary glands black; there are numerous ecchymoses in the mucosa, some in the cæcum being one to two centimetres in diameter.

Liver weighs 40 ounces; capsule smooth, rather cloudy. Under the capsule are a few small pale-yellowish areas. Section shows anæmic glistening surface; tissue soft; acini not distinct; the larger vessels have greenish walls. Cut surface shows a few small, indistinctly outlined, yellowish nodules.

Along the whole length of the vertebral column, from the neck to the pelvis, there is a green, smooth layer under the serous membrane. In the thorax the layer is more than one centimetre thick, and becomes thicker at the insertion of the diaphragm. The mass is continuous with the periosteum, in fact replaces it; the vessels and nerves pass through it. On section it is firm, smooth, in places showing bands of white fibrous tissue, vessels, and nerves. This mass extends on the ribs and intercostal muscles for some distance under the costal pleura. On the abdominal vertebræ it is thin, appearing only as a thickening of the periosteum.

Pericranium thickened and of bright green color. Under the temporal muscles are bright green masses, filling the space between the periosteum and the thinned temporal muscle. Section of the tumors shows homogenous structure, hard and moderately dry.

The dura is greenish, the bone not altered. The walls of all the venous sinuses are thickened and show a green color, like the other parts described, though not quite so bright. The sinuses contain pale-greenish clots.

The brain shows no change beyond extreme anæmia.

On removing the roof of the orbit, the cavity is found filled with a solid green mass, which separates easily from the bone in some places, leaving it smooth. On cutting through the tumor, the bulb is found loose in the front part, the vessels, nerves, and muscles running through the mass. Remains of the periosteum and connective tissue are seen only at the sphenoidal end of the orbit; most of the connective tissue and fat of the orbit is replaced by or converted into the greenish material.

The spinous processes and laminæ of the vertebræ are covered with similar greenish material, the green color passing for some distance into the fibrous tissue running into the dorsal muscles. On opening the spinal canal the dura is found unaltered, but the periosteum is thick and greenish-gray. The most remarkable thing in this part is the transformation of the loose fat of the spinal canal, which is totally converted into soft, greenish masses, some of them several centimetres in length, and having only a loose connection with the dura. Many of these show small reddish areas on section. The cancellated part of the sternum in different places, of the ribs, vertebræ (bodies, spinous processes) and skull, was pale and dry-looking, but apparently healthy; pieces of each were removed for microscopic examination.

For sections, pieces from various organs were hardened in alcohol (95 per cent. and absolute), Fleming, platinum chloride, sublimate, and Mueller's solution. Parts prepared for showing the nuclear structure were hardened by Prof. W. H. Howell, but, owing probably to post-mortem changes, did not give good results. On the whole, pieces hardened in alcohol gave the best results. Sections were cut unimbedded, in celloidin and in paraffin, and stained with alum-carmine, hæmatoxylin and eosine, safranine and *licht-Grün* (Benda), and hæmatoxylin and orange G.[1]

Unimbedded sections were also stained by Gram's method and with methylene blue with negative results so far as bacteria are concerned. Sections were also cut from some of the tissues in Mueller's fluid, the day after the autopsy, on the freezing microtome, and examined in the fluid.

The growth shows the same general characteristics in all parts of the body. It is made up of round or roundish cells, somewhat larger than those of a lymph nodule, which they resemble. They lie in a vascularized reticulum. The reticulum varies in character in different parts of the body, and even in different parts of the same section. In some places it is very fine and in fine meshes, in others the fibres are coarse and the meshes larger. The coarser fibres are evidently fibres of the original connective tissue of the part, as their relations show.

The reticulum showed best in fresh frozen sections with the cells shaken out, and closely resembled that of a lymph gland. Unfortunately, these were not kept, and the drawing made by Dr. Huber, from a hardened section, which was very difficult to pencil, gives a less satisfactory picture than the fresh material. (See Plate: figure A.)

The amount of fibrous tissue varies according to the seat of the growth. Along the vertebræ it is quite extensive, while in the spinal canal there is an extremely fine reticulum with no fibrous septa or bands.

Connective tissue in all places shows a predilection for the new growth.

In the green masses the nerve-sheaths and the adventitia of veins are entirely replaced by lymphoid tissue. The adventitia of arteries is involved, though less completely.

The vascular supply of the growths is usually extensive, and consists of vessels of old and new formation. The arteries seem to be those of the original tissue, but the accompanying veins are often so involved in the growth, and their lumen so altered by growths in their walls, that it is difficult to recognize them. There are, besides many vessels having only an endothelial lining and a thin fibrous, or probably, in some cases, muscular wall, the latter closely surrounded by the new growth. Lymphatic vessels are numerous and in many places show dilatations, or open out of cystic cavities filled with colorless corpuscles, and sometimes containing a small proportion of red blood cells. Some of the cavities are as much as two to three millimetres in diameter, lined by endothelial cells and filled with cells like the others described.

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[1] Paraffin sections were stained by Dr. G. C. Huber, assistant professor of histology, by the two latter-named methods, but no mitoses could be found. Dr. Howell intended to study the pieces from the point of view of blood formation. As this was prevented by his change of location, Dr. Huber kindly took up that part of the subject, but with negative results, though he devoted an amount of time and care to the matter that can only be appreciated by those who have done similar work.

The cells, as mentioned above, are round, or sometimes longish, but never spindle-shaped. They have a small amount of protoplasm—in places almost none; in others, especially in the denser connective tissue, the nucleus occupies about two-thirds the diameter, with finely granular protoplasm around it. The cells in the growth do not differ in their appearance from those in the bloodvessels. They show no evidence or degeneration. Spindle cells are found only along the vessels. "Mastzellen" appear in excessive numbers in various organs in or near the new growths.

The topographical and other peculiarities of the growths not yet described can best be studied in connection with the different tissues examined.

In the orbit the growth extends from the bony walls to the bulb and eyelids, and involves all structures but the optic nerve and bulb. The periosteum shows, to the naked eye, only in the posterior part, but microscopically it can be seen that the inner (bone) layer is not at all infiltrated. In some places the bone separates easily, in others it is closely adherent (decalcified sections). A few fat cells are left in the mass, but almost all the fat and connective tissue is replaced by lymphoid tissue. The nerves lie in masses of the tumor without any trace of their sheaths. The adventitiæ of the smaller arteries and of the veins have disappeared. The sheaths of the muscles in many places are replaced by the new growth, and in many places there is round-celled infiltration between the bundles of muscle fibres. In many cases the intra-muscular septa are infiltrated, while the sheath at the same level is not involved.

The growths in the dura and sinus longitudinalis are also developed from the external layer of the membrane (as is the case in all parts). The microscopic appearance of the dural tumors is rather different from that found in other parts, in the greater amount of connective tissue. This is so arranged as to give a slightly fasciculated appearance. In many places there are long narrow spaces between lines of hard fibrous tissue, filled with round cells, and causing an appearance similar to that in inflammations in fibrous tissue, or in the infiltration around a carcinoma or the wall of an old cavity. The vascular supply of the tumors in the dura is very much less than in other situations.

The thick masses along the bodies of the vertebræ resemble those of the dura in the frequent appearance of a fasciculated arrangement. In the middle of the mass this resembles carcinomatous structure, though the cells are of the same lymphoid form as in other places. The alveolar-looking part is inconsiderable, and around it the tissue has a lymphoid appearance, varied according to the bands of original connective tissue, vessels, and nerves running through it. Nerve-sheaths and adventitiæ are entirely replaced by lymphoid tissue. In many places the walls of the veins are filled with round cells, so that the lumen appears only as a narrow Y-shaped slit. Channels and irregular cavities lined by endothelial cells and containing cells like those of the new growths are numerous. In the loose connective tissue between the dense mass and the pleura there are scattered groups of cells, less numerous and smaller near the pleura.

The pleura is extensively involved, so that it is difficult to find places where there is no round-celled infiltration. In some parts this causes thickenings visible to the naked eye. These have the same structure as in other parts. Often there is an abrupt boundary between lung and new growth, but in other places the lymphoid tissue passes into the lung, replacing it more or less completely. The borders of the infiltration are not well defined, the septa being thickened for some distance around the denser infiltrate by numerous round cells. In some parts, in the vicinity of the new growths, there are catarrhal, œdematous, and hemorrhagic areas.

The growth in the temporal region shows very interesting relations. It is confined between the deep layer of the pericranial and the temporal fascia and muscle. Beginning at the upper border as a narrow layer between the two membranes, it becomes thicker toward the middle of the muscle, where it reaches a thickness, in the hardened specimen, of 1 cm. Nearer the inner surface the growth is without trace of muscle fibres. Farther away from the bone isolated fibres are encountered, very narrow, but still showing transverse striæ, and nuclei which stain well. These are separated by lymphoid tissue, but still farther away the fibres are closer together. Finally, just under the temporal fascia, is a layer of muscle fibres 1 mm. thick, with very little infiltration, but with an excessive amount of connective tissue, as if many fibres had disappeared. The new growth has a fine reticulum. Spindle cells are rare. The vessels exhibit the same characteristics as described in other parts.

On the spinous processes the periosteum shows no infiltration close to the bone. The fibrous origins of the dorsal muscles are densely packed with lymphoid cells, sometimes extending far out between the muscles (at least 1 cm. from the bone). The walls of the vessels are infiltrated in many places.

The lymphatic glands examined were those from the mesentery, the only ones which showed enlargement. These show marked hyperplasia. The medullary sinuses are not to be recognized as such, being uniformly filled with cells like those in the nodules, but not quite so closely packed. The fibrous septa and reticulum are not hypertrophied.

The spleen shows areas of lymphoid hyperplasia which pass gradually into tissue that is almost normal. The hyperplastic areas are sometimes as much as 5 mm. in diameter. These, like the similar change in the lymph glands, cannot be distinguished from those in sections of the same organs from cases of leukæmia.

The larger mass of the thymus shows only a slight infiltration of lymphoid cells in the septa and an increase of cells in the central parts of the nodules. The long narrow process extending up to the cricoid is made up of a narrow strip of almost normal tissue, passing abruptly into lymphoid material which shows no trace of the original relations. The extremity of the process, which contained a small greenish tumor, has a very thin capsule but no septa. The peripheral part is made up of lymphoid tissue of uniform structure. The tumor can be recognized by its closely packed cells, which lie in a fine reticulum. This central part lies loosely in an irregular cavity, the borders of which are formed by lobular masses the size and shape of thymus nodules. In some places the two parts have no connection, but in others the tumor passes into the adjacent structure. In the central part, and in the extreme periphery of the gland, the cells are round, but in a narrow zone at the edge of the cavity described, the cells are long and lie in long, narrow spaces between fine lines of fibrous tissue. There are a few Hassall's bodies in the peripheral part. In other words, all the fibrous tissue of this part of the thymus has undergone lymphoid change. In all parts dilated lymph channels and cystic spaces filled with lymphoid cells occur.

Numerous sections of the bone-marrow were stained and examined by Dr. Huber with negative results. In some places there seems to be an increase of lymphoid cells, but after careful examination I think Dr. Huber's idea that these are in the vessels is correct.

The liver shows a scanty infiltration of lymphoid cells in various parts, without definite relation to the zones of the acini. In some places the cells are more closely aggregated around the central vein, in others in the portal areas, especially in the connective tissue and the walls of the portal vein. In some places small lymphomatous areas occur. These are not sharply circumscribed. At their magins the capillaries are dilated and filled with (leukæmic) blood. Farther in, no liver cells are to be seen, the original tissue being replaced by the lymphoid growth.

In the kidneys the epithelial cells, including nuclei, are well preserved. In the boundary zone or the pyramid near it are a few lymphoid areas, not more than 3 mm. in diameter. The smaller ones are mere diffuse infiltrations. The larger ones show masses of lymphoid tissue between the tubules. The parts of the tubules between the new tissue appear normal, but at the sides the tubules are compressed and their cells atrophied. In the cells of the branches (especially ascending) of Henle's loops, also perhaps in the collecting-tubes, in the pyramids, are fine greenish-yellow, glistening granules, sometimes scattered, sometimes in small masses. Rarely, yellow granules are seen in the intertubular tissue. The yellow pigment occurs in only in a few places, and apparently has no relation with the infiltrations. The parts sectioned show no hemorrhages.

The supra-renal bodies are normal. In the fat around them the walls of the vessels show round-celled infiltration. In the stomach there is an unusual quantity of lymphoid tissue at the base of the tubules. In many places the intertubular tissue contains an excess of small cells, and in some places, just beneath the surface, these cells form large masses extending over areas of several millimetres.

The most obvious features of the case are those relating to the tumor-formation, and they relegate it at once to the category of chloroma as described by systematic writers. (See the works of Birch-Hirschfeld, Ziegler, and Klebs.)

The first mention I can find of a case of this kind is by Allan Burns (*Observations on the Surgical Anatomy of the Head and Neck.* By Allan Burns. 1st Am. ed., Baltimore, 1823, p. 386). The history of the case is not given in full.

The patient was a young man who had a tumor in the left orbit, with protrusion of the eye, followed by loss of vision and destruction of the eye. Later a similar growth appeared in the right orbit. The patient had paralysis of the lower extremities and bladder and died about three months after the beginning of the disease.

After death, tumors were found in the orbits which were supposed to have grown from the lachrymal glands. At all events those glands were diseased. There were tumors on the frontal bone, in the frontal, ethmoidal, and sphenoidal sinuses, the nose and the dura mater, with thickening of the periosteum and dura, caused by deposits of a peculiar greenish-yellow substance having a cartilaginous hardness and containing more or less fibrous tissue.

Burns thought the disease one *sui generis*. "The series of parts affected and the mode of propagation were different from what is generally met with in fungus hematodes or medullary sarcoma."

The next case was reported by Balfour (*Edin. Med. and Surg. Journ.*, 1835, xliii. p. 319), of Edinburgh, in 1834, as one of peculiar disease of the skull and dura mater.

In 1836, Durand-Fardel (*Journ. hebd. des Prog. des Sci. Méd.*, Paris, 1836, t. iii. p. 207) reported a case. He cited the case of Balfour, the only similar one known to him, but said there was a third observation of the same kind in the *Revue d'Edimbourg*. It was impossible for him, as it has been for me, to find an account of it.

Dittrich, of Prague (*Prag. Vierteljahrsschrift f. die prakt. Heilk.*, 1846, Bd. ii. p. 104), in 1846, at the autopsy of a woman who died with symptoms of scorbutus, found "dirty green" tumors on the periosteum of the vertebræ, ribs, and cranium, and also in the kidneys and ovaries.

In 1853, King (*Monthly Journ. of Med. Sci.*, Edin., August, 1853, vol. xvii. p. 97), of Glasgow, under the title of "A Case of Chloroma," reported the details of a case seen in 1849, having symptoms much like those in my own, but with the tumors limited to the head. Models and preparations of this case were placed in the Museum of Anatomy in the University of Glasgow.

In 1854, Aran (*Arch. gén. de Méd.*, 5. sér., 1854, t. iv. p. 385) reported a case seen in 1851, and made it, with the cases of Balfour, Durand-Fardel and King, the subject of an anatomical and clinical study. The same case was published by Lebert, who made the microscopic examination, in his *Traité d'Anatomie Pathologique* (Paris, 1857, i. 323, plate xlv., figs. 1 to 4), with illustrations of the growths. These two articles served to call attention to the subject and form the first landmark in its literature. It seems proper here to correct a wrong impression concerning the name chloroma. Most of the German writers, following Huber, speak of Aran as the author of the name. But King's article, with the word in the title, appeared fourteen months before that of Aran. The latter distinctly says (*loc. cit.*, p. 386): "M. King, a publié dans un journal Anglais, en lui donnant le nom de chloroma," etc. Aran gave "cancer-vert" as the synonym for chloroma. It is not a little curious that King does not use the name in the body of his paper, so seeming to indicate that it was already in use, but I can find no previous application of the term.

Mackenzie (*A Practical Treatise on the Diseases of the Eye*, by Wm. Mackenzie, M.D., Philadelphia, 1855) at least as early as 1855 had a section on chloroma in his chapter on the Diseases of the Lachrymal Glands, and cited a characteristic case seen by himself in the Glasgow Eye Infirmary in 1830–'31. Mackenzie spoke of a similar case reported by Williams (*Med. Gaz.*, London, 1849, xliv. p. 854. See also *Path. Trans.*, ii.). A careful study of the latter makes it certain it was not one of chloroma, and the same remark is true of the cases of Sir E. Home, referred to in another place (*loc. cit.*, p. 970) by Mackenzie.

In 1855, Hillier (*Trans. Path. Soc. of London*, 1855, vii. p. 337) reported a case to the London Pathological Society. This is spoken of as a case of recurrent tumor of the orbit, and its resemblance to the chloroma of Mackenzie mentioned.

In 1866, Dressler (*Arch. f. path. Anat.*, etc., 1866, Bd. xxxv. p. 605) described a case of the same kind in a letter to Virchow. The case occurred in 1860, in Prague. Dressler was not aware of the case of Dittrich.

No other example was seen, apparently, after that until 1878, when the occurrence of an example in Thiersch's clinic gave the late Carl Huber an opportunity for a thorough anatomical and clinical study of all the cases known to him. (*Arch. der Heilkunde*, 1878, xix. p. 129.)

Since then instances have been more frequently observed. In 1882, Behring and Wicherkiewicz (*Berlin. klin. Wochenschrift*, 1882, No. 33, p. 509) reported one from Posen; Waldstein (*Arch. f. path. Anat.*, Bd. xci. p. 12) one from Heidelberg in 1883 (in this case leukæmia appeared late in the disease). In the same year Chiari (*Prag. Zeitschr. f. Heilk.*, 1883, Bd. iv. p. 177) reported a third case in Prague. In 1884, Gade *Nord. Med. Arkiv*, Bd. xvi. No. 19, and *Comptes-rendus*, xvi., No. 22, p. 20) reported a new case with an analysis of the cases known to him, ten in number. The year after, Von Recklinghausen (*loc. cit.*) mentioned he had seen a case, and raised the question of the leukæmic nature of chloroma. Finally, Höring (*Arbeiten aus d. Path. Anat. Inst. zu Tübingen*, Bd. i. Heft 1, p. 180), in 1891, reported a case from the Tübingen clinic.

My own case raises the total to seventeen, those of Burns, Mackenzie, and Hillier having been overlooked before. There are, perhaps, cases recorded not published. Hamilton in his *Text-book*, says (i. p. 506): "The author has several times met with a peculiar soft, light green-colored tumor, situated in the anterior mediastinum, usually attached to the posterior aspect of the sternum. It had all the appearance [microscopic?—D.] of a round-cell sarcoma, but had a quite remarkable green color (chloroma)." Unfortunately no other particulars are given (I shall mention later cases that are either the same as or closely related to chloroma).

In all the cases the most obvious point in common is the peculiar color, which suggested the name chloroma or cancer-vert. The precise tint was probably not the same, making due allowance for difference in nomenclature. Thus, Burns makes it "greenish-yellow;" Balfour, "bright olive green;" Durand-Fardel, "vert pomme très foncée;" Dittrich, "dirty-greenish;" King, "yellowish-green" (his plate shows a dark green); Aran, "gris-verdâtre" or "gris-vert;" Mackenzie, "light greenish or whey color;" Hillier, "yellowish green;" Dressler, "light green;" Huber, "dark yellowish-green;" or, in fresh (operation) specimens, "exquisite light yellowish-green;" Behring and Wicherkiewicz, "beautiful dark grass-green;" Waldstein, "pea-green or darker;" Chiari, "light green;" Gade, "vert-jaunâtre to vert-grisâtre;" Höring, "yellow or greenish-yellow," or "ziemlich reines grün." In my own case the color could be best described as pea-green. It was much like the tint shown in the plates of Chiari and Dressler; not so dark as King's or Lebert's. It differed, however, in various parts, so that some were pale sage-green, others darker, or again with pink, brown, or red stains. The small growths in the liver and kidneys were almost white, but in the pancreas and thymus the color was distinctly green, though pale. The color gradually faded from the preserved specimens. Owing to the fact that the solutions were frequently changed, it is impossible to tell whether the color was dissolved out or bleached.

The cause of the color still remains unknown. Balfour, without making any examinations, supposed it to be due to some pigment allied to bile coloring matter. Dittrich attributed it to putrefaction, which was plausible, though in my case, as well as in some others, as also in the parts removed during life in Huber's case, such an explanation is impossible. King had part of the tumor and the spirit in which the specimens were kept examined by Dr. R. D. Thompson, who reported that "he could find no trace of bile, the only source from which green coloring matter could emanate in the human system so far as we know at present." He quoted the opinion of Lebert, that a greenish color could arise from a local infiltration of a peculiar kind of fat. (Lebert, *Physiol. Pathologique*, ii. p. 122). King also speculated as to the possibility of the color being due to the altered extravasated blood, but noted that old and recent tumors had the same shade of green. Aran and Lebert did not venture to explain the nature of the coloring matter. Virchow, in his comments on Dressler's case, said the color was diffused in the tissue without granular or crystalline deposits. This was in tissue which had been dried, so that the conditions were different from those in other cases. Huber was the first to make careful investigations into the nature of the color. Without describing his methods in detail, suffice it to say that he ascribed the color to certain fine molecules found in the cells, which he thought were allied to, if not really fat. This opinion was shared by Chiari on account of the reaction of the granules seen by him to alcohol and ether and to osmic acid. Chiari says, and the explanation is plausible, that in Huber's case the granules were so small as to be recognized with difficulty. In his own this was not so, and the recognition of the fatty nature of the granules was easy. Chemical examinations by Huppert proved the coloring matter to be one hitherto unknown in the human organism. Höring came to conclusions identical with those of Chiari. Behring and Wicherkiewicz claimed to find in the tumors in their case an unusual proportion of chlorine. They were led to make the analysis from having found that tough sputum containing many desquamated cells and inspissated pus when treated with chlorine became grass-green.

Waldstein thought the coloring matter a derivative of blood. From Langhans's experiments (*Arch. f. path. Anat.*, Bd. xlix. p. 102 *et seq.*) it might be supposed that the color was due to altered extravasated blood. The following facts oppose this: The green color under the microscope is not so distinct as Langhans described it; it occurs often when there is no other sign of old extravasation; in parts (spinal fat, intestines) with numerous extravasations there is neither more nor less color than in other places, except red stains from orange-red granules, which occur in the altered spinal fat. Examinations by Otto in Gade's case showed an absence of both bile and blood-coloring matter, so that Gade shared the opinion of Chiari and Huber, that the color was dependent on fatty granules. Opposed to this view, and impossible to reconcile at present, are the negative results Von Recklinghausen had by the use of osmic acid. The latter held that the color was a parenchymatous one. He compared it, as did Huber and Dressler, with that of old pus, making this one of his reasons for believing the color parenchymatous (as Virchow had done).

Not knowing at the time the difference of opinion, I lost an opportunity for having examinations made by an expert. The idea I had from the literature, that the pigment was of a fatty nature, seemed confirmed by the abundant, highly refracting granules which were certainly present in the cells in the fresh frozen sections. In sections examined later, after the tissue was decolorized, the granules were absent. I also thought that the peculiar color was simply an exaggeration of the greenish tint so common in the blood-clots and the neoplasms of leukæmia. The finding of greenish-yellow pigment in the renal epithelium in Chiari's case and my own seems to me to oppose the idea that these were fatty, since in my own case, though the green tumors have long been bleached, sections of the kidney from specimens more than a year in absolute alcohol show as much pigment as ever. The pigment must be altered in some way in the kidneys, if it be really the same as that which gave color to the fresh specimens. Our knowledge of such pigments is so imperfect that the whole subject must be left to future investigations.

In other physical characteristics, the chloromatous tumors exhibit points of resemblance. The consistency varies from a gelatinous or soft elastic (Aran) to a firm cartilaginous (Balfour, Burns). Most frequently it is described as moderately firm or brawny (Dittrich, Höring, Huber).

In my own case, I could find all the different degrees of hardness, from a soft elastic in the orbit, or very soft and gelatinous in the spinal canal, to dense cartilaginous hardness along the vertebræ.

The cut surface is described by various writers as homogeneous, with or without fibrous septa, depending on the seat; and this, too, was to be seen in my case.

In some cases, a turbid greenish juice could be produced by scraping the cut surface (Aran); in others the juice was scanty and colorless (Huber), or thick and creamy (Dittrich), or the tissue was almost dry (Höring). These characteristics, as also the presence of a moist lustre (Behring and Wicherkiewicz, Huber), depend on the seat of the growth and the firmness and vascularity of the tissue in which it develops. In my case the tissue in the orbit, more so that in the spinal canal, was moist and yielded much juice, that along the vertebræ and on the pleura was almost dry.

The external surfaces of the tumors were smooth or nodular—tumors proper, as distinguished from uniform infiltrations, being usually nodular.

In regard to the seat of the growths, we find most interesting data. In all the cases reported some part of the head was affected. In twelve cases the scalp contained greenish deposits; in fifteen the dura, in thirteen the orbit, in eleven, various parts of the periosteum of the face. Less frequently we find the green substance in the periosteum of the vertebræ and the ribs adjacent (five cases); under the temporal muscle (five); bone-marrow (four); liver (four); kidneys (eight); spleen (three); mesenteric glands, stomach, intestines, pleura, lungs, heart and pericardium, mediastinum, submaxillary and cervical lymph glands, nares, pharynx, testes, ovaries, prostate, lingual tonsil, bronchial lymph glands, pancreas, thymus, pelvic connective tissue, broad ligament, skin, mammary gland, internal and external ears, in eye at insertion of optic nerve. (In several cases the examinations were not complete.)

The marked predilection of the periosteum, especially that of the head, has been noticed by all observers, and most of them look on some part of the periosteum of the head or face as the starting-point. So Huber, in whose case tumors were first noticed in the mammary gland, believed the primary disease was in the head. It does not seem possible, either from the histories or post-mortem records, to show a common point of origin, as in the orbit. Burns thought the disease primary in the lachrymal gland. Mackenzie examined King's specimens, and concluded, as did King, that the disease began in the periosteum of the lachrymal fossa, affecting the gland secondarily.

The predilection is not for periosteum alone, but for fibrous tissue in general, as strikingly exhibited in my own case.

In regard to the histological structure of the growths, we must bear in mind the fact that we cannot accept without criticism the names given by writers of more than a generation ago, for we know, from what has been said, that the growths belong to a class which has been the subject of endless controversy and change of name. Interesting as it would be to quote the histological descriptions of different writers on the subject, the recital would carry this paper to an inordinate length, and the necessity is less urgent from the fact that the recent literature is easily accessible.

The new growths are sarcomatous, in the sense that they are "connective tissue formations, with excessive development of the cellular elements." (Virchow, *Path. Geschwülste,* ii. p. 177.) Taking the most obvious view, that they are periosteal sarcomata (metastatic periosteal sarcoma, Huber), we find certain points of difference from the usual conditions in such tumors.

There is an absence of bone formation. It is true, some of the older writers (King, Aran) mention spicules of bone in the tumors. But these were found only when the bone was usured, and the process was probably more like that which occurs in many diseases affecting the nutrition of the bone than that which takes place in myelogenic sarcoma.

There is an absence of polynuclear giant cells, so common in periosteal sarcoma. The cells found in different cases agree closely in size, shape, and appearance.[1]

The difference between the myelogenic form of periosteal sarcoma and chloroma can best be explained by the fact that the latter develops from the outer layer of the membrane. Lücke[2] has, indeed, figured a periosteal sarcoma having a lymphoid structure, but it is not identical with the growths we are considering.

Again, chloroma differs from other forms of periosteal sarcoma in the absence of a tendency to form fibro-sarcomatous structure. The only descriptions that seem to contradict this statement come from the earlier days of less exact technique. In scrapings the spindle cells and original fibrous tissue would be more striking than in sections. The fibrous tissue in all cases carefully examined was that of the original tissue.

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[1] Although a minor point, it seems necessary to speak of an apparent contradiction to the above statement. Virchow (Path. Geschw., ii. p. 220) says that Lebert (loc. cit.) "pictured large polynuclear cells ('grosse vielkernige zellen,')" etc. Lebert certainly has a figure (4) which looks something like a giant cell. In the text, however, he says the cells measured from 10 to 20 mm. in diameter, and nowhere mentions polynuclear giant cells. The figure, therefore, represents a number of cells.

[2] Die Lehre von den Geschwülsten, etc. Pitha-Billroth's Handbuch, p. 196.

In view, however, of certain clinical features observed in cases of chloroma, but even more so on account of the tendency of pathological knowledge, we must go beyond the diagnosis of sarcoma, since this has long been a collective name, including neoplasms of the most diverse kinds. We must make an attempt at a more distinctive histological classification, and must endeavor to learn something of the nosological and etiological relations of the growth. The latter is of the greatest importance, for we know that on the ground of causation we have separated a number of diseases from the category of sarcoma.

As regards the first point, my studies lead me to coincide with Von Recklinghausen[1] as to the lymphomatous structure of the growths. Höring, Chiari, and Behring, and Wicherkiewicz, all describe the tumors as lymphomatous in structure. Huber, too, described the tumors in his case as made up of cells lying in a network similar to that of the lymph glands, but not so regular and delicate.

Waldstein, who was led by the clinical features of his case to look at it from a new standpoint, called the growth chlorolymphoma, and declined to consider it a sarcoma. In some respects Waldstein went too far. Thus, he rejected the idea of sarcoma especially on account of the structure of the tissue, and the fact that nowhere else in the body could secondary tumors be found. So far as the statement regarding the structure is concerned, it is impossible to understand it literally. The assertion in regard to metastases seems strange in the light of Waldstein's description of greenish-colored lymph glands ("zwar nicht wesentlich vergrössert,") in the porta and behind the stomach, and a greenish discoloration of the dura and inner surface of the cranium, not to mention a walnut-sized green mass in the mediastinum. Waldstein, however, explained all this by saying the tumor was simply a hyperplastic lymph-gland, and the color due to numerous small and large hemorrhages. He thought the discoloration of the dura and the bone marrow could be explained by the fact that during life the urine was green-colored, though why the discolorations were so localized he did not explain. The peculiar fact about the urine is interesting in connection with the finding, in Chiari's case and my own, of a peculiar pigment in the kidneys. In my case the urine did not have a greenish tint, nor did it show any peculiar color reactions.

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[1] Von Recklinghausen said (loc. cit.): "More important than the green color is the pure lymphomatous structure, which appears in all the cases reported. Besides this is the multiple appearance of the growths noted in all except the imperfectly reported cases, and the distribution over the larger part of the tissue which stands in most intimate relation to the lymph system."

Höring has criticised Von Recklinghausen for saying that the lymphomatous character of the tumors was made out in all cases of chloroma, and says this cannot be accepted in the face of the belief of Virchow, Huber, and Chiari that the tissue was sarcomatous. If that were good reasoning we should have to call Aran's tumors "cancer," Hillier's "fibro-cellular," etc. It is most unfortunate that Virchow could examine the specimens only after they had been dried for years. Almost three years elapsed between the time when Virchow referred to Lebert's case and that of his examination of Dressler's specimens, and from the remarks appended to Dressler's letter it does not appear that Virchow recalled the "famous case" of Aran (*Path. Geschw.*, ii. p. 220).

Not only from later authors do we find various reasons for assuming the lymphomatous character of chloroma, but, as far as we could expect, from earlier ones also. King, for example, says the tumors showed a mass of irregular granules, some of a round, others of an oblong shape, mingled with imperfect fibres or fine filaments.[1]

Aran's and Lebert's descriptions prove that their growth had a structure identical with the others.

Hillier described the tumor as a combination of the fibro-cellular and fibro-plastic. In other early cases, although we have no microscopic examinations to depend on, the other features of the tumors agree so closely that we have every right to view the growths as Von Recklinghausen did.

The idea that other forms of tumor may have the characteristic color of chloroma cannot be said to be groundless, but so far we can say that all the cases described as chloromatous agreed histologically. The remarkable case of Bock (*Arch. f. path. Anat.*, Bd. xci. p. 442) forms, I believe, a unique exception to the above statement. In that case the green color was due to biliverdin. The growth was adenomatous, though Bock called it sarcomatous simply because it was anomalous. The case evidently has little right to the term "chlorom," given in the "register" of the journal in which it was published.

The tumors can best be described, I think, as lymphomata, in the original sense (Virchow, *Path. Geschw.*, ii. p. 563). This seems less likely to lead to misunderstanding than terms like lympho-sarcoma or lymph-adenoma.

The lymphoid structure of the tumors is the principal thing in making the distinction, for although the similarity of lymphoma and lympho-sarcoma, histologically, is increased by the finding (Arnold, *Arch. f.*

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[1] A criticism of King's description by Huber is based on a misconception of the word "areolar" in the then commonly used sense of connective tissue. Huber supposed it to indicate an alveolar arrangement ("areolares Gefüge").

path. Anat., Bd. xcviii. p. 506; Ribbert, *Ib.*, Bd. cii. p. 452; Klebs, *Allg. Path.*, ii. p. 673) of giant cells in simple hyperplastic lymph glands and lymphomata, their absence, as in chloroma, I look on as a point to be observed in the differentiation. This, of course, may not be a constant feature of chloroma, but, like all other distinguishing points between the two forms in question, becomes of use in cases lying at the extremes.

But for the present I think we cannot do better than continue to use the term "chloroma," and some synonym, as lymphoma, lymph-adenoma, lympho-sarcoma, or myeloma, could be used to express peculiar features or the views of the reporter.

In endeavoring to classify a tumor of this kind we have a striking evidence that the histological structure is not enough. It would be a waste of time to bring up other examples to illustrate this statement. What is necessary to complete our knowledge is the establishment of the etiological relationship of the growth. So far, attempts to solve this have been fruitless. In the meantime we can perhaps increase the chances of improving our outlook by examining the clinical characteristics of the cases.

The analysis of the cases I have gathered agrees in the main with those of Huber and Gade; but on account of the larger number of cases, as well as some features I wish to emphasize, I give my results.

Chloroma is most frequent in early life—the average age of fifteen cases being 15.26 years. Another is described as a young man (Burns); Von Recklinghausen does not give the age in his case. The youngest was four years old (Dressler); and seven were under eight. But that the disease is not limited to the very young, follows from the fact that five were over twenty, one twenty-eight, and one forty-four years (Waldstein).

In six cases females were affected; males in ten.

The course of the disease is short. The average duration in twelve cases in which it is given is five months. In one (Balfour) the patient is said to have been sick for two or three years, but active symptoms were observed only during a few months. But although in many cases the course of the disease was brief, in that of Durand-Fardel the patient was sick two years, having very abundant hemorrhages for eighteen months. In my own case I have used three months in making the table, but here, as in Balfour's case, the course must have been longer.

Exciting causes are rarely given. In Chiari's case the disease began with toothache, and the tumor first appeared in the site of the extracted tooth.

The fact that three cases were observed in Prague, three in Glasgow, and two in Paris seems worth noting.

The family and previous histories were usually good. Balfour noted, however, a phthisical family history; Hillier's patient was delicate, and

Durand-Fardel's was of lymphatic temperament, and sick four years with frequent catarrhs and hemoptysis.

Early symptoms were as follows: Pallor, 6 cases; emaciation, 3; nose-bleed, 3; "scorbutus," 1; petechiæ, 1; loss of energy, 2; fever, 1; frequent pulse, 3; headache, 3; tinnitus aurium, 2; deafness, 7; double vision, 1; loss of vision, 2; exophthalmus, 6; facial paralysis, 2; feeling of oppression, 1; prominence of temples, tumor of mammary, feeling of constriction, toothache, each 1. (Many cases were treated in eye or surgical clinics, and only the special histories are available.)

Symptoms occurring later are: Thirst, fatigue, strabismus, double vision (in addition to those noted before), deafness, otorrhœa, pain in epigastrium, dyspnœa, abscesses, anemia, œdema, hemorrhages from lungs, intestines, in skin, and from the nose, obstruction of the nose, fever, frequent pulse, nephritis, irritability, coma, delirium, convulsions, wasting, constipation, vomiting, involuntary stools, diarrhœa, anorexia, pain in the region of the liver, craving for meat (King, Dock), disgust for meat (Aran), enlargement of spleen (two, probably four, cases), swelling of thyroid.

Death usually occurred from profound exhaustion, inability to take food, and often with some of the nervous symptoms mentioned above.

This brief synopsis shows the great resemblance, clinically, of chloroma and leukæmia and pseudo-leukæmia. It is not within the scope of the present paper to consider at length the relations of leukæmia and pseudo-leukæmia. A great deal of valuable work has been done on the subject in the past few years, with the result of showing that certain cases of so-called pseudo-leukæmia represent an early ("aleukæmic") stage of leukæmia. All of them await the discovery of the etiological factor to make their relations clear. (Without wishing to make invidious distinctions, I refer to papers of Dreschfeld, *British Medical Journal*, April 30, 1892, p. 893; *Deutsche med. Woch.*, 1891, No. 42, p. 1176; Westphal, A. D., *Arch. f. klin. Med.*, Bd. li., Heft 1; editorial, *Medical News*, Phila., February 18, 1893, p. 191.)

It is necessary, however, to consider certain features of the cases before claiming more than a resemblance between the diseases named. I refer to deafness, exophthalmus, and the condition of the blood, for the other symptoms are common to many processes, the differential diagnosis of which is quite unnecessary.

As explanations of the deafness noted so often, in the cases of Durand-Fardel, Aran, Behring and Wicherkiewicz, and Gade, greenish masses were found in various parts of the internal or middle ear, in several others in the external auditory canal. In other cases the ears were not examined.

Deafness has been noted in leukæmia, and although in some cases, as that of Pepper (*Medical and Surgical Reporter*, 1883, xlviii, February

24, p. 197) it might be ascribed to hemorrhage, on account of its temporary character or sudden onset, in others it was due to the presence of leukæmic tissue in the ear. Politzer appears to have been the first to bring forward anatomical evidence of the latter (Otol. Congress, Basel, 1884, *Comptes-rendus*, p. 139). Later (*Arch. für Ohrenheilk.* xxiii. p. 242), Gradenigo reported a case of sudden deafness in leukæmia, partly disappearing. Post-mortem, there was evidence of chronic inflammation and old hemorrhages, with leukæmic growths in the mucous membrane of the tympanum. Gradenigo explained Politzer's case in the same way, believing the chronic inflammation a predisposing cause for leukæmic growths in the ear, and contrasted the tendency to hemorrhage in the eye in leukæmia with that of chronic inflammation of the ear in the same disease.

Exophthalmus was present in thirteen of the seventeen cases of chloroma. It was double in eleven. This, of course, depends on the involvement of the orbital periosteum and Tenon's capsule, which are affected not quite so frequently as the dura (and not always in continuity). The exophthalmus is, therefore, caused in the same purely mechanical way as in other tumors of the orbit, some of which, especially glio- and round-celled sarcoma, are not infrequently bilateral.

Exophthalmus has been described in leukæmia, and this is especially interesting from the fact that lymphoid tissue has never been seen or described in the orbit in health.

Leber (*Arch. f. Ophthalmologie*, 24. Jahrg., 1878, Abth. 1, p. 195) reported the case of a man of forty-eight years, with a leukæmia in which the red and white corpuscles were in almost equal numbers. Most of the leucocytes were small ones. There were large tumors on the eyelids, not adherent to the skin, going back into the orbit and not adherent to its margin. Both eyes were prominent. Under the conjunctiva tumors could be seen, having a dirty brown to violet color, as had those under the lids. There were swellings under the temporal muscles, which could not be distinguished from bone by the touch. There was hemorrhagic retinitis. The urine contained albumin and granular casts. The skin was pale; there was emaciation.

A bit of tissue removed from under the conjunctiva was soft, somewhat gelatinous. Microscopically, it showed closely aggregated mono-nuclear round cells in a delicate, wide-meshed, fibrillary connective tissue, not very well vascularized. The lymph glands in the neck were enlarged; the manubrium somewhat thickened and painful. There was great weakness, pain in the head, at times convergent squint, and thirst. The tumors in the temporal region became larger; the liver reached to the umbilicus; the spleen was enlarged. Exophthalmus increased, the swelling over the sternum reached the size of a fist, and tumors appeared in the parotid and submaxillary region. The patient died fourteen months after the tumors appeared in the orbit and six months after the leukæmia was recognized. No autopsy was made.

The resemblance of the case to most of those of chloroma is remarkable. Leber thought the tumors in the temporal region were from the bone-marrow, as I did in my own case, though every surgeon knows how deceptive the hardness of a tumor often is.

Leber quoted the case of Chauvel (*Gaz. hebd.*, 1877, No. 23) which was similar to his own in many respects, but in which the blood was not examined, though leukæmia was suspected.

Osterwald (*Arch. f. Ophthalmologie*, Bd. xxii., Abth. 3, p. 203) reported a case from Leber's clinic which is even more important in connection with chloroma than the preceding. The patient was a boy of four years. In April, 1881, a slight paralysis of the face appeared, and then receded. Then exophthalmus developed, flat swellings appeared in the temporal regions, the skin became cachectic, and there was loss of appetite. By May 25th there was double exophthalmus, dilated veins, and submucous hemorrhages; the tumors in the temporal region measured four to five by three to four centimetres in extent.

Leukæmia being suspected by Leber, the blood was examined and red and white corpuscles found in the proportion of 3–4 : 1. There was emaciation, and anæmia of skin and mucous membranes; on the skin a few petechiæ (flea-bites?). The skin bled easily; the blood was unusually thin and watery. No glands enlarged, except those behind the angles of the jaw. The liver extended two cm. beyond the costal margin; the spleen could not be felt. There was no pain or tenderness over the sternum. Later there was œdema of the eyelids; epistaxis; fever; pulse frequent, later slow, small, soft, and thready; tonic flexor contractions, tremors, and death, after repeated nose-bleed, three months after the beginning.

At the autopsy, flat, yellowish, "almost pus-colored," and tolerably firm neoplasms were found on the cranium, along the sutures. On the frontal were softer and reddish tumors. There were tumors in the walls of the transverse and cavernous sinuses and on the dura, of yellowish green, "durchaus eiterähnlichen" color, but hard. There were also areas of atrophy of bone, with osteophytes. At the base of the brain, and in the convolutions of the Sylvian fissure and optic thalamus, were hemorrhages.

There were ecchymoses all over the surface of the heart, under the pleura, and in the lung. The spleen weighed 71 grammes; it was soft, of pale brown color. The liver weighed 760 grammes. There were petechiæ in the stomach; the epigastric lymphatic glands were large, partly of greenish-yellow purulent appearance. There was also slight swelling of the mesenteric glands. The axillary glands were enlarged. On the ribs and along the vertebræ were leukæmic growths. The marrow of the ribs and right femur were of a brownish-green color and soft consistence. The diagnosis was myelogenic leukæmia, with leukæmic neoplasms as the cause of the peculiar symptoms.

Leucocytes occurred especially in two forms: most of them were of 1½ to 2½ times the diameter of a red corpuscle; the others the size of, or smaller than, red corpuscles.

The growths in various parts showed a leukæmic or lymph-adenoid character. Fibrous tissue varied in amount in different parts. (Osterwald reported the case especially as an example of the bacterial origin of leukæmia, for which see the original article.)

Birk (*St. Petersburger med. Wochenschr.*, 1833, viii, p. 377–86; *Fortschr. der Med.*, 1884, p. 138) has also reported a case beginning with intermittent fever, weakness, headache, swelling of liver and spleen. The lymph glands became enlarged; there was pain over the sternum. Examination of the blood showed a ratio of 1 : 3. The colorless cells were smaller than the red corpuscles, with few exceptions.

Exophthalmus came on suddenly, in both eyes, with loss of sight. Both testes became swollen; double pleural effusion came on, and after the appearance of œdema of the lower extremities the patient died. After death uniform infiltrations were found in various parts of the body. The exophthalmus was due to the formation of "new-formed lymph glands in the posterior part of the orbit."

Arnold and Becker (*Archiv. f. Ophthalmologie*, Bd. xvii.) and Bernheimer (*Bericht üb. die Heidelb. Ophthal. Gesellsch.*, 1889, p. 199; *Centralbl. f. allg. Path.*

u. path. Anat., 1890, p. 211) have reported cases of localized lymph-adenoma of the orbit. In a case reported by Kelsch and Vaillard (*Annales de l'Inst. Pasteur*, iv. 276) diagnosed *intra vitam* as leukæmia, but probably not entitled to that name, lymphoid tumors formed under the eyelids. It might be supposed that the lymphoid tissue could take its origin from the so-called "trachom" glands of the eyelid, but at least in the cases of so-called leukæmia with orbital tumors such an origin seems out of the question. (In regard to orbital lymphoid tissue, see Zaluskowski, *Arch. f. mik. Anat.*, Bd. xxx. p. 316.)

The case of Osterwald, even to the color of the new growths, is so like those of chloroma that it might seem proper to include it among the latter. For obvious reasons I have not done so. In the cases of Birk and Leber there is strong reason to suspect chloroma, but in the absence of more exact knowledge it is just as useful to keep them among leukæmic cases, showing, as they do, the peculiar localization of the chloromatous tumors.

In all cases in which the general condition of the patient is described, anæmia was marked. In a number of cases conditions closely related are described. So, in King's case there were petechiæ in the very beginning, and even at that time a slight blow caused severe hemorrhage; ten days later a blow on the face caused extensive extravasation as low down as the clavicle. By the end of the fourth week it was noted that health had failed. There were hemorrhages under the conjunctivæ, the skin (in a previously healthy "country-looking" girl) clear and bloodless.

In Aran's case there was early epistaxis, which was abundant every day for two weeks. There were anæmic murmurs over the heart and in the neck, and remarkable general anæmia. Aran spoke of the disposition to hemorrhage in his analysis of cases.

In the case of Durand-Fardel there was nose-bleed for eighteen months before admission. The skin was puffy and waxy and very anæmic.

In Mackenzie's case there was nose-bleed twice.

Balfour noted a bloody effusion under the conjunctiva.

Dittrich, whose case is reported chiefly from the post-mortem point of view, speaks of symptoms of "scorbutus." The body was pale, with few post-mortem discolorations; the blood like meat-water.

In Huber's case the patient was pale and anæmic; the cadaver pale, with few post-mortem discolorations.

In Chiari's case there was hemorrhage in the retina (but also new growths in the bulbs).

In Waldstein's case there was great anæmia early, and leukæmia appeared shortly before death.

In my own case all the blood symptoms noted, except characteristic scorbutic signs, were present.

In addition to Waldstein's case and my own, in which the proportion of red and white corpuscles were those found in leukæmia, Huber noted in his own case, post-mortem, that in the blood, "in addition to the usual elements, among which the leucocytes were decidedly increased ('entschieden etwas vermehrt'), there were bodies which in all respects corresponded to the cells found in the new growths."

In regard to nose-bleed, it might be supposed the bleeding was due to pressure on the veins, but no other evidence of congestion was present. A similar explanation might be advanced for the retinal hemorrhage, but here again other evidence of obstruction is absent. In Leber's case of leukæmia, as in my own of chloroma, there was no choke-disk.

We have found, then, that in chloroma we have new growths which are like those of leukæmia, and which occur in the organs affected by those in leukæmia, either primarily or secondarily. We find, also, a complexus of symptoms which agrees, not only in its broad and striking features but also in detail, with that of the other condition. Three out of the nine cases examined since leukæmia was known show an increase of the leucocytes, two of them an increase such as is seen usually only in leukæmia. In the other cases no blood examinations were made, and we know that it is quite possible for a leukæmic blood to present no appearance that would attract attention. That makes the resemblance of chloroma to leukæmia greater, but there are two things that prevent us from going farther and claiming identity. These are, the short time in which increase of leucocytes has been observed in chloroma, and the unsatisfactory status of the term leukæmia.

Whether the increase of colorless corpuscles came on late, or was present during a longer period in my own case and in Huber's, can never be known. In Waldstein's case it was very late.

In rapidity of course, in general, chloroma stands between ordinary cases of leukæmia and those described by Ebstein (D. *Arch. f. klin. Med.*, Bd. lxiv. p. 343) as cases of acute leukæmia, one of which was Waldstein's case of chloroma. (The view advanced in the article just cited, that there is an essential difference between acute and chronic leukæmia, still requires confirmation.)

Chloroma also has a shorter course than is the rule in pseudo-leukæmia, but in the latter, too, we find exceptions.

Here, again, the possibility of a transition like that which is seen sometimes when leukæmia develops in the course of pseudo-leukæmia must be borne in mind, being exemplified in chloroma in the case of Waldstein's.

The greatest obstacle in attempting to show the possible relations of chloroma and leukæmia depend on the facts that we have so little knowledge of the anatomical basis and the clinical limitations of the latter.

Virchow's prophetic "Ich vindicire für die farblosen Blutkörperchen eine Stelle in der Pathologie" ("Weisses Blut und Milz Tumor," 1. Art., *Med. Zeitung*, 1846, Aug.-Sept., Nos. 34–36, and *Abhandlungen zur Wiss. Med.*, 2. ed., 173) has been followed by countless researches in the physiology and pathology of those bodies, and yet in the almost half-century that has elapsed how much more do we know than is contained in the following (*ibid.*, p. 192)?—"Leukæmia is not merely a purely anatomical, but essentially also a pathological conception. Not merely is the simple fact of the increase of the colorless corpuscles expressed, but, at the same time, the deficiency of red corpuscles, or, as I have emphasized from the beginning, the altered tissue formation of the blood in its dependence on certain organs."

We have, to be sure, learned much regarding the clinical features of leukæmia, and have widened its pathological anatomy, but our knowledge of its essential nature is not far from that expressed in the statement that it is "an albinism of the blood." (Virchow, *loc. cit.*)

Up to a very recent time the increase of the leucocytes was almost all that was needed to make the diagnosis. That is, the original idea of Virchow, that the difference between leukæmia and other conditions with increase of leucocytes—termed by him leucocytosis—depended on the permanence of the former (Virchow, *Path. Geschw.*, ii. p. 566, and *Cell. Path.*, Am. ed., p. 205: "Leukæmia is thus a sort of permanent progressive leucocytosis," etc.). But as more was learned of the transitory leucocytes, it was found that their differentiation, early or late, was not always easy. The attempt was then made to fix an arbitrary line between leucocytosis and leukæmia, and the idea of Magnus Huss, proposed long before (*Arch. gén. de Méd.*, 1857, ii. p. 308), to make the diagnosis when the proportion of white to red rose to 1 : 20 or more, was so eagerly taken up by clinicians that it seems to have answered a universal demand, which indeed it did—the demand for diagnostic signs. But like so many of them, it was found unavailable either to make a diagnosis or to confirm one when most needed. (Huss himself said the sign was to be used only when others—swelling of spleen and cachexia—were present.)

A new era opened when Ehrlich (*Zeitschr. für klin. Med.*, i., H. 3, p. 553, and *Farbenanalytische Untersuchungen zur Hist. u. Klinik des Blutes* Th. i. p. 51), announced that "an absolute increase of the eosinophile cells took place in leukæmia," or, as expressed in another place (Schwarze, *Inaug. Dissert.*, Berlin, 1880, and *Farben. Unters.*, p. 94): "The only pathological process in which the eosinophile cells are increased in mentionable manner is leukæmia. When one considers that the usual methods of examination frequently leave us in the lurch when the question between extreme leucocytosis or leukæmia arises, and when one considers that the beginning of this disease is almost beyond our diagnosis, the discovery (*Auffindung*) of eosinophile cells must be recognized as a grateful enrichment of our diagnostic methods."

The hope aroused by these statements, which were abundantly investigated, proved to be illusory, for many observers found an increase of eosinophile cells in various conditions quite different from those claimed by Ehrlich, and found them diminished (see below) in cases of leukæmia. But even before the observations alluded to were generally known, Erhlich, through his pupil Spilling (*Inaug. Dissert.*, Berlin, 1880, and *Farb. Unters.*, p. 71), admitted that the appearance of mononuclear cells with neutrophile granules was more distinctive than that of either the eosinophile cell or the "Mastzellen" (which Ehrlich had at one time looked on as important).

Still later (*Char. Annalen*, Bd. xii., and *Farb. Unters.*, p. 129), Ehrlich repeated this claim for the mononuclear neutrophile cells, though limiting their appearance to cases of myelogenic leukæmia ("Da nach meinen Erfahrungen die geschilderten mononucleären neutrophilen Zellen beim Erwachsenen unter keinen Umständen im Blut erscheinen, stellen sie das feinste und sicherste Reagent einer auf leukämischer Basis beruhenden Myelæmie dar, die auf diesem Wege schon in den ersten Anfängen mit Sicherheit erkannt und von jeder andersartigen Vermehrung der Weissen Blutkörperchen unterschieden werden kann.") At that time Ehrlich still claimed that the increased appearance of eosinophile cells was an additional sign of the same disease, " as the only place of formation of the cells in question is in the bone-marrow, "although he admitted, as before, their occurrence in normal blood.

Soon after this, Müller and Rieder (" Eosinophilen Zellen im circulirenden Blut,"*Arch. f. klin. Med.*, Bd. xlviii.), not only confirmed Ehrlich's claim regarding the mononuclear neutrophile cells, but went much farther. In the first place they identified Ehrlich's cell just named with the "Markzelle" of Müller, which the latter had in an earlier article shown to be the same as the myelocyte of Cornil, "cellule medullaire." (*Arch. f. klin. Med.*, Bd. xlviii., p. 47 *et seq.*)

While Ehrlich claimed his cell to be diagnostic of myelogenic leukæmia, Müller and Rieder held it to be so of leukæmia in general (*loc. cit.*, p. 119). "It is probable," they continued, "that the bone-marrow is always affected (a view which v. Ziemssen has also defended), although a slight change can easily be overlooked. We are therefore at present of the opinion that myelocytes will be found in all cases of leukæmia, even in the so-called lymphatic form."

In these two articles Müller and Rieder called attention to the important fact, previously overlooked, or not correctly estimated, that the eosinophile cells in leukæmia were remarkable more for appearing in unusual forms than in increased numbers.

They also gave the results of observations, confirming the earlier ones of Neumann (*Berl. klin. Wochenschr.*, 1878, No. 41, pp. 607 and 608), Cafavy (*Lancet*, 1880, ii. p. 769), and Löwit (*Sitzungsber. der kais. Akad.*

in Wien, 3. Abth., May, 1887), in regard to the diminished amœboid motion of the leucocytes on leukæmic blood in the warm stage, and suggested this as an additional diagnostic point.

Very soon after giving out the statements regarding the myelocytes, Müller had reason to modify them. In a case of lymphatic leukæmia, in which, by the way, eosinophile cells were present only in the proportion of one to several thousand, the myelocytes were so scarce that Müller was led to believe that "in many cases of lymphatic anæmia they could be entirely absent." (*Arch. f. klin. Med.*, Bd. l. p. 55.) The possibility was exemplified by a case observed by Rieder. This was a case of rapidly fatal lymphatic leukæmia, in which the proportion of white to red corpuscles rose to 1 : 12 (red 3,700,000). Most of the cells (about 90 per cent.) were lymphocytes. A very few normal eosinophile cells were found, but no myelocytes. There were, also, no nucleated red corpuscles. No myelocytes could be found in blood-forming organs, nor were mitoses present. The bone-marrow presented lymph-adenoid hyperplasia (Neumann). (Rieder, *Beiträge zur Kenntniss der Leukocytose, etc.*, Leipzig, 1892, p. 38 *et seq.*)

It seems important to lay these facts briefly before the reader, on account of the confusion surrounding the subject and the necessity of indicating the difficulties attending the interpretation of the case under consideration. It seems important, too, because from the history of the eosinophile cell we may expect the myelocyte to be used, on the grounds of the early reports, long after its original advocates have changed their opinion as to its value. In fact, there is a distinct tendency even now to carry not only the diagnostic but also the pathognomonic value of this cell to an extreme not warranted by the facts. (I have not thought it advisable to mention in the body of the paper that the theory of Müller of the origin of the myelocyte is by no means universally accepted. Hayem, Löwit, and Troje (*Berlin. klin. Wochenschr.*, 1892, No. xii. p. 285), hold ideas opposed to those of Müller and differing among themselves. (The works of v. Limbeck, Rieder, and Hayem, and the articles cited above, can be referred to.) Recently Wertheim has brought forward, though very modestly it must be said, another cell claiming to be important in leukæmia—a spindle-shaped leucocyte. This must be even less distinctive than any other cell claimed to be specific (*Zeitschrift für Heilkunde*, 1891, pp. 308, 314).

From what has been said it might seem that the search for a specific cell in leukæmia has brought us back to our original position. But in the meantime we have learned some things that should make our disappointment thereat less keen. For this we have really to thank Ehrlich, whose painstaking and ingenious investigations have made possible all that has been gained, and who should, if for no other reason, not be held responsible for all that has been said in his name.

The advance alluded to is indicated in the following attempt to formulate a description of leukæmic blood:

It has a diminished number of red corpuscles, some of which have nuclei (normoblasts usually), though in some cases of lymphatic leukæmia there are no nucleated red corpuscles. The leucocytes are increased, usually to an extreme degree, and the increase is constant, though in some cases even great variations occur. The colorless corpuscles, in most cases, are characterized by the altered proportion of mono- and polynuclear forms, by the appearance of eosinophile cells in unusual numbers and of mononuclear neutrophile cells (Ehrlich, myelocytes, Markzellen of others). In some cases eosinophile cells and myelocytes are absent, or the former, if present, few in number (lymphatic leukæmia). *Most frequently and most characteristically, the cells vary more in size than those of the same classes in normal blood and in the so-called leucocytoses.* The leucocytes, especially the abnormal forms, show less active amœboid motion on the warm stage than usual. Less characteristic elements of leukæmic blood are poikilocytes, macro- and microcytes, "Mastzellen," karyokinetic figures in normal or abnormal cells, and Charcot's crystals (on standing).

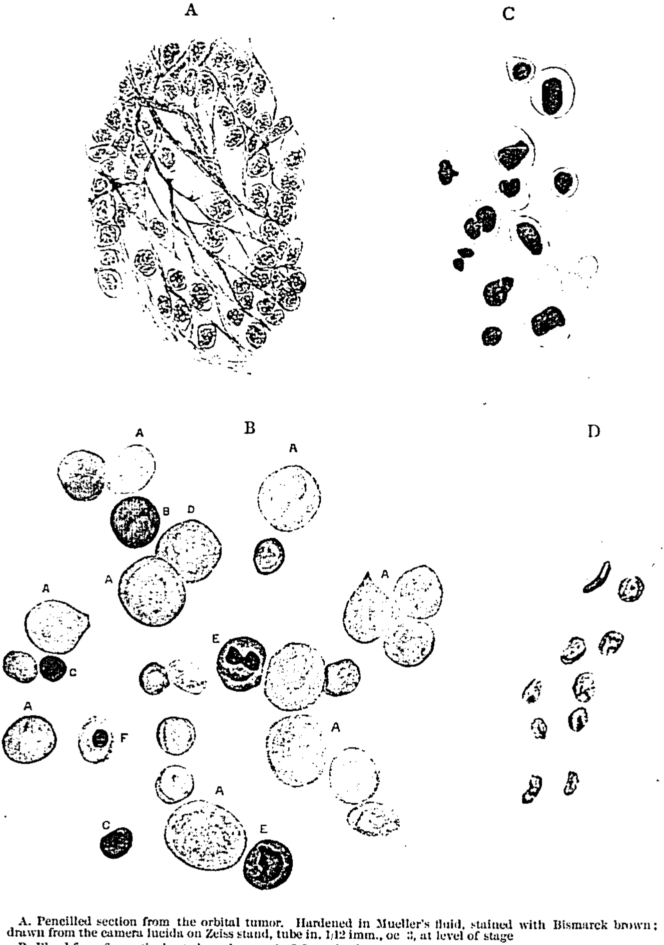
This statement, which agrees in the main with the conclusions of Rieder (*loc. cit.*, p. 36), is based on a careful analysis of the recent literature of leukæmia, and the examination of several cases of that disease.

The difference in size of the corpuscles seems important. In a case of lymphatic leukæmia, in which small lymphocytes formed almost all the leucocytes, the only eosinophile cells found—not more than one in many hundreds—were not more than half the average size found in healthy blood.

In two cases of splenic-myelogenic and three of myelo-splenic leukæmia the very small and very large polynuclear forms were very striking. These are found in the (human) marrow in non-leukæmic diseases, but not, I believe, in the blood. With our present means of investigation, we must give up the idea of finding a new and specific cell in leukæmic blood.

The distinction between leukæmias depending on disease of one or another blood-forming organ, or of combinations of organs, cannot be made from the blood alone, although very accurate guesses can be made in some cases, especially by taking the other conditions into consideration.

The attempt to separate the lymphatic form of leukæmia from the others cannot yet be said to have been successful. Notwithstanding the difference presented in some cases, not only by the blood, but also by the clinical symptoms (rapid course), on the other hand, in other cases the usual clinical picture is presented; and transition forms and combinations occur so often that the unity of the leukæmic process cannot yet



A. Pencilled section from the orbital tumor. Hardened in Mueller's fluid, stained with Bismarck brown; drawn from the camera lucida on Zeiss stand, tube in, 1/12 imm., oc 3, at level of stage

B. Blood from finger-tip, heated one hour at 120° C., stained with methylene blue and eosin. *a*, *b*, large lymphocytes; *c*, small lymphocytes; *d*, large mononuclear; *e*, polynuclear; *f*, normoblast. The leucocytes were drawn from the central part of one field; the normoblast introduced from another field; only a few of the red corpuscles were drawn. Zeiss, 1/12, oc. 4, tube in; drawing 17 mm. below the stage.

C. Blood corpuscles in pulmonary vein (lung section). Hardened in absolute alcohol, cut in paraffin, stained with hæmatoxylin and orange G. Same conditions for drawing as in B. All the leucocytes in one group, but only three red corpuscles were drawn.

D. Renal tubule with greenish-yellow pigment. Hardened in alcohol, cut unimbedded, stained with alum-carmine. Amplification as in B.

be abandoned. The statement regarding the size of the leucocytes applies only to those fixed in a thin layer—all the cells flat. In a layer in which rouleaux have formed, wet or dry, the largest cells may not seem larger than red corpuscles.

From the above it would appear that we should be able to recognize leukæmia in the earliest stage; but so far, I believe, this has not been done. Practically, we can see how tedious the necessary examinations might be.

We do seem, however, to have reached a stage at which we can claim to have criteria for developed leukæmia, though even for this we must await the confirmation that only time can give.

With this necessary digression, we can return to the consideration of my own case of chloroma, and study the blood, the characteristics of which, I believe, are peculiar.

The most striking forms are the large lymphocytes, which occur in the proportion of 65 per cent. These are from the diameter of a red corpuscle to three times that width (see Plate: figure B, *a*). In hæmatoxylin (Delafield's), they take a pale greenish-blue color; in methylene blue a pale blue, and in Ehrlich's "triacid" appear as clear spaces with hardly any color. Only the smaller ones (see Plate: B, *b*) stain well, though not so deeply as the small lymphocytes. These cells show no distinction between nucleus and protoplasm. Some of them take the methylene blue more strongly in narrow areas around the edge—not complete rings. In the fresh blood, these cells do not seem nearly so large as when dried.

Small lymphocytes occur in the proportion of 7 per cent. These vary slightly in size, as shown by the figure (B, *c*), stain well in all nuclear stains, are homogeneous or coarsely granular, and show (with hæmatoxylin-eosin only) a very narrow rim of protoplasm.

Normal mononuclear and transition forms are present to the extent of 8 per cent. (1½ and 6½). They vary much in size. The nuclei of the transition forms usually stain well, those of the mononuclear less strongly. Mononuclear cells with neutrophile granulations cannot be distinctly made out. Out of a large number of covers stained with a mixture (Ehrlich's) that gave brilliant results with other specimens, Dr. Huber could find only three that were even suspicious. I thought I found two, but am very doubtful. They certainly were not typical.

Polynuclear cells form about twenty per cent. of the leucocytes. Their nuclei stain well, but the granulations are not as distinct as in normal blood. The cells of this class show the greatest variation in size. Those in the Plate (B, *e*), show the mean or normal; many are not more than half that diameter, a few are larger.

Normoblasts occur in proportion of two to five per thousand of red corpuscles (B, *f*).

Only one eosinophile cell has been found, out of many thousands of leucocytes. This was found by Dr. Huber, who with great patience carefully stained and examined a large number of imperfectly spread cover-glasses. I have recently gone over a large number of preparations without finding one more.

No mitoses can be found.

The proportion of white to red corpuscles, from a large number of fields counted is 24.74 : 100.

Certain points regarding the blood require special consideration.

The most numerous form of leucocyte is the large lymphocyte, the individuals of which vary considerably in size from those found in normal blood. They differ also from the latter in that, almost without exception, they show no protoplasms around the nucleus. This characteristic does not appear in the cells of the same class hardened in the bloodvessels. Figure C in the Plate was drawn with the same lenses and at the same level as B. It is easy to recognize in it the various kinds of leucocytes found in the fresh blood. In tissues hardened in various ways the results are the same so far as this feature is concerned. It seems rational to think that the peculiar conditions regarding the cells under consideration represent degenerative phenomena, although that does not advance our knowledge.

The small lymphocytes are increased, though not enough for us to say they exceed the normal limit. These cells differ so markedly in size and intensity of coloring from the large ones, that is easier to draw the line between them than in ordinary cases. Many of them look like free nuclei, especially the nuclei of normoblasts, but with hæmatoxylin and eosin a narrow rim of protoplasm may be made out. They never show the "grating" appearance.

The characteristics of the polynuclear and mononuclear cells have been sufficiently described. It is interesting to note the negative point, that the large cells of these classes having a faintly staining or clear protoplasm are very scarce.

The nucleated red corpuscles are all normoblasts. The large proportion of these cells is interesting in connection with other peculiarities of the case. In many respects this resembles lymphatic leukæmia. In the case of Rieder, mentioned before (*loc. cit.*, p. 40), no nucleated red corpuscles were found. Hayem (*Du Sang*, pp. 860, 864) has described a case of lymphatic leukæmia (red, 3,720,000; white, 476,200) without nucleated red corpuscles. Müller, in the case alluded to, found them, though few. In his case there was lymphoid bone-marrow. Wertheim (*Zeitschrift f. Heilkunde*, 1891, Bd. xii., p. 314) in a case of lymphatic leukæmia found none. (In this case the blood-count was —red, 2,525,000; white, 480,000, *i. e.*, 5.2 : 1; hæmoglobin, 55 per cent.). Thayer (*Boston Med. and Surg. Journ.*, February 23, 1893, p. 184) says that in lymphatic leukæmia nucleated red corpuscles are rare, and when present are often megaloblasts. (See Neumann, *Arch. f. Heilk.*, 1872, xiii. p. 507.)

It has been supposed that nucleated red corpuscles only occur in cases of leukæmia in which the bone-marrow is involved, but this seems irrational (see opposing statements of v. Limbeck, *Grundriss einer klin. Path. des Blutes*, 1892, p. 161, and Bizzozero and Salvioli, *Centralbl. f. d. med. Wiss.*, 1879). That the appearance of these cells depends on an irritation of bone-marrow in the sense of Ehrlich ("Ueber schwere anæmische Zustände," *Verh. des XI. Cong. f. in. Med.*, 1892, Sep. Abdr.,

p. 13) can easily be granted, but as both Neumann and Müller found these bodies in the liver in large numbers it is by no means necessary to assume that.

The almost total absence of eosinophile cells is noteworthy, because it too is common in the lymphatic form of leukæmia, but even more so because the eosinophile cell appears to be a normal constituent of blood. I have examined in vain for a case in which they were as scanty as in this one and in a case of lymphatic leukæmia alluded to above. Guttmann (*Deutsche med. Wochenschr.*, 1891, No. 43, p. 1201) has mentioned a case of lymphatic leukæmia in which the spleen was also affected, in which only a single eosinophile cell could be found in a preparation. Wertheim (*loc. cit.*) found none. Müller in his case of lymphæmia (*loc. cit.*) found very few. Thayer (*loc. cit.*) in one case found only 0.1 per cent.

The absence of cells with basophile granulations in the blood, and their existence in the tissues in increased numbers, is interesting.

The absence of Charcot's crystals—the blood and pieces of liver and spleen were kept until putrid and examined daily with negative results—is another interesting feature in this case, especially in connection with the absence of other signs of disease of the bone-marrow.

The proportions of red and white corpuscles are worth emphasizing. Although it is true in many cases that in lymphatic leukæmia the increase of leucocytes is not so marked as in other forms, it is often considerable. In the cases of Müller, Wertheim, Hayem, and Guttmann already quoted, the proportions were 1 : 6, 1 : 5 2, 1 : 8, 1 : 1.4.

We find, then, in chloroma, blood which in its altered character coincides with that found in leukæmia. The conclusion is obvious, but before drawing it, it is necessary to consider another phase of leukæmia —that expressed in the words, "the altered tissue-formation of the blood in its dependence on certain organs."

It is often forgotten that we do not as yet know the origin of the leukæmic leucocytes, any more than of the normal ones. Efforts to explain the origin of leucocytes by facts observed in leukæmia, as might have been expected, have not made the subject any clearer, for observations have been interpreted in diametrically opposite ways.

The theory most widely accepted is that originated by Virchow and widened by Neumann, viz., that the leucocytes in leukæmia are derived from certain (hyperplastic) organs regarding which it is supposed, as the result of other observations, "that they stand in a certain relation to the formation of blood." These organs are the spleen and lymphatic glands and the thymus (Virchow, *Path. Geschw.*, ii. p. 566), and the bone-marrow (Neumann, *Centralbl. f. d. med. Wiss*, 1869, *Arch. f. Heilk.*, Bd. xi., *Berl. klin. Wochenschr.*, 1878, Nos. 6, 7, 9, 10).

The value of the evidence in favor of the splenic and lymphatic origin of leucocytes can be gathered from the fact that by many the bone-marrow is looked on as the chief or only source of the excess of leucocytes in leukæmia.

This view or combination of views of the matter stands in direct contradiction to that of Kottmann (" Die Symptome der Leukæmie," *Inaug. Dissert.*, Berne, 1871), Biesiadecki (*Wien. med. Jahrb.*, 1876, p. 233), Löwit (*Sitzungsb. der k. Akad. in Wien*, 1885, Bd. xcii., Abth. 3), and others.

Notwithstanding the ingenuity and expertness with which Löwit defends his view, there can be little doubt that the view of Virchow-Neumann, at least in its broad outlines, will ultimately be shown to be correct.

But the latter view has been enlarged along with the increase of ideas of blood-formation, in the acceptance of the myelogenic form of leukæmia, and if we admit a participation of the organs mentioned, we must also admit the possible participation of the other known lymphoid tissues, the innumerable peripheral lymph nodules of the body. (See Flemming, *Arch. f. mik. Anat.*, Bd. xxiv.)

This brings up an interesting aspect of leukæmia, that relating to the so-called metastatic or heteroplastic growths, the history of which has been one of change.

Virchow originally (*Path. Geschw.* ii. p. 568), looked on these as heteroplastic neoplasms, so that "a sort of lymphatic tumor developed in organs in which normally no such formations occurred." The supposition that these were due to deposits of cells from the blood was rejected by Virchow, who held they originated *in loco*, as undoubted new formations.

But under the irresistible influence of the emigration doctrine Virchow's idea lost ground. This was hardly to be wondered at when men could go so far as, *e. g.*, Rindfleisch (*Lehrb. der path. Gewebelehre*, 1886, 6th ed., p. 211), who claimed a resemblance between leukæmic heteroplastic tumors and hemorrhages, though he held also that active emigration had some part in the process.

Bizzozero (*Arch. f. path. Anat.*, Bd. xcix. p. 378), however, revived the old teaching when he showed that active mitosis was going on in the secondary leukæmic tumors. His observations have been confirmed by Müller (*Arch. f. klin. Med.*, Nos. 48 and 50), and Wertheim (*loc. cit.*), and with the reaction now going on in regard to the extent of emigration in general, the true relation of the secondary leukæmic tumors is likely to be accurately determined.

Although it was believed very early (Virchow, Friedreich) that part of the leucocytes in leukæmia came from the secondary growths, but little importance has been attributed to those growths by later writers. Recently, indeed, if he is correctly reported, Virchow (*Berl. klin. Woch.*, 1892, No. 12, p. 289) has stated that the growths have no importance in the production of leucocytes, and that they are formed only in the latter part of the disease. The question of early or late appearance seems to me to be a relative one, though it is true as a rule that the leukæmic lymphomata occur late in the disease.

But in regard to the possibility of some of the leucocytes being derived from the lymphomata, I think we must admit that the evidence is quite as strong as that regarding the origin of leucocytes from the spleen, thymus, bone-marrow, or peripheral lymph nodules.

Moreover, in many instances, it is difficult or impossible to say whether a given lymphomatous structure is hyperplastic or heteroplastic. In fact, when we consider the obscurity surrounding the development of the lymph nodules, when we remember that we do not know whether the lymph corpuscles are formed by division of similar ones in the nodules (Flemming), or are derived from the cells of the reticular tissue (Baumgarten), or the endothelium (Ribbert), and when we consider not only the possibility, but the strong probability of the origin of lymphocytes in the lymph spaces, we can see the need of a reconsideration of the secondary lymphomata.[1]

From what we do know of the natural history of leukæmia and of chloroma we can see the analogies of the diseases. We can say that chloroma is a lymphomatous process similar in its clinical features to leukæmia and pseudo-leukæmia. Our ignorance of its precise relations depends partly on the fact that our knowledge of chloroma is very incomplete, partly on the indefinite nature of leukæmia and pseudo-leukæmia. Whereas in leukæmia and pseudo-leukæmia there is for the most part a hyperplasia of the lymphoid tissue with which we are most familiar, in chloroma there is hyperplasia, perhaps heteroplasia of tissue closely related to the others, but even less understood.

In endeavoring to learn more of chloroma we find ourselves facing problems of the greatest interest, but problems that at present cannot be solved.

In my own case the insignificant enlargement of the lymph glands, thymus, and spleen (the latter two being involved only by localized neoplasms), seems incapable of accounting for the large numbers of leucocytes. It is impossible to say that the bone-marrow was not altered, since all the bones were not examined, but on account of the condition of the blood and from the results in other cases we can exclude such a complication with much confidence. We can hardly avoid the conclusion, therefore, that the source of a large part of the leucocytes must have been the chloromatous growths. A careful examination of hundreds of sections of vessels of various kinds in the green tumors convinces me that no difference can be made out between the majority of the colorless corpuscles in the blood and lymph vessels and those in the adjacent lymphoid tissue.

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[1] The point just alluded to must be worked out without reference to differences between the lymphocytes and other leucocytes in circulating blood. The recent investigations into the rôle of the fixed cells in inflammation, especially those of Ziegler and his pupils, the renewed interest in the connective tissue or lymph-space corpuscle, the "dormant" cells of Shakespeare (Medical News, Philadelphia, 1882, vol. xl. 1), and "Schlummer Zellen," of Grawitz (Arch. f. path. Anat., Bd. cxxvii., and Berl. klin Wochenschr., 1892), open up a promising field in all lymphomatous diseases.

If we assume that the cells have wandered out from the vessels we must suppose the excess of leucocytes was either produced in the vessels, or in blood-forming organs apparently little diseased. Moreover, the cells are such as least easily pass through vessel walls actively, and if forced through passively we should at least find many polynuclear cells in the tissue, which is not the case.

The absence of mitoses does not invalidate the supposition that the cells in the tumors have formed there (Bizzozero, *loc. cit.*).

To designate the cases as lympho-sarcoma adds nothing to our knowledge. Although it is no longer believed, as it was at the beginning, that in lympho-sarcoma there is never an increase of leucocytes in the blood, it is better in any case in which such an increase does occur to separate it from the category of sarcoma. Nor is it a gain to throw such cases in a distinct group along with those of lymphatic leukæmia, unless efforts to separate the lymphocytes from the other leucocytes genetically, are more successful in the future than they have been in the past, and even then the etiological factor might be a common one.

Looked at from every point of view, it seems better to class chloroma, for the present, along with leukæmia, pseudo-leukæmia, and myeloma, and to endeavor to work out its anatomical and clinical features on the same lines as those necessarily followed in the others.

Comparing chloroma with ordinary cases of leukæmia or pseudo-leukæmia, one cannot but be struck by the resemblance of the former to the process in those cases in which an insignificant epithelial tumor, primary in the uterus, gall-bladder, or intestines, produces early and enormous secondary growths in many organs.

Again, there is a striking resemblance to infectious (parasitic) processes. So long as we do not know whether leukæmia, as ordinarily met with, is due to vegetative excesses originating in the organism, or to irritants (parasites) from without, it is idle to speculate at length.

The clinical aspects of chloroma call up the possibilities of an infectious origin, which, of course, was suspected for leukæmia at the very beginning. In the case of Osterwald, which I strongly suspect to be one of chloroma, it was claimed that micro-organisms were found; but here, as in most of the cases of leukæmia and pseudo-leukæmia in which similar claims were made, the evidence is insufficient.

The symptoms of chloroma are so striking, and in many respects so uniform, that it is not only possible to make a diagnosis during life, but in about half the cases it should be possible to do so at a very early period.

The important points in the diagnosis are: The appearance, usually below the age of twenty, of anæmia without evident cause, with loss of strength, dyspnœa and emaciation; hemorrhages in skin, mucous membranes (epistaxis), or internal organs (retina); rapid pulse; ocular symptoms, such as difficulty of vision, strabismus and especially exophthalmus, without the special features of Basedow's disease and with tumor in the orbit; deafness and ringing in the ears; and tumors under the temporals, or on the cranium in other parts, or in other parts of the body. Before the appearance of tumors the diagnosis would be doubtful, but after the appearance of tumors in the orbit and under the temporals, it could be made almost with certainty.

In such cases the blood should be examined by all the methods known, either to detect an increase or alteration of leucocytes already present, or, if that be not found, examinations should be made at short intervals in order to observe the possible advent of a leukæmic condition, which might come on only a short time before death.

The spleen, liver, lymph glands, and bones should be examined with reference to alteration in size and tenderness.

Although the essential points in the diagnosis were laid down by Huber, in no subsequent case was the disease thought of before death. It is to be hoped that, by calling attention once more to the subject, later cases may receive investigation directed to the elucidation of the many points yet unsettled.

THE ANATOMY OF THE VERMIFORM APPENDIX.

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I desire to call attention to some of the surgical relations which this now important portion of the intestinal tube makes with its surroundings—based upon the examination of 74 bodies in the dissecting-room of this college.

The points which presented themselves to my mind were:

1. The position of the vermiform appendix in relation to the ileum.
2. Its relation to the colon.
3. The relation of the colon to pelvic cavities.
4. The length of the appendix.
5. The distance from the anterior superior spine to the base of the vermiform appendix.